A Stochastic Thermostat Algorithm for Coarse-Grained Thermomechanical Modeling of Large-scale Soft Matters: Theory and Application to Microfilaments

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ABSTRACT: As all-atom molecular dynamics method is limited by its enormous computational cost, various coarse-grained strategies have been developed to extend the length scale of soft matters in the modeling of mechanical behaviors. However, the classical thermostat algorithm in highly coarse-grained molecular dynamics method would underestimate the thermodynamic behaviors of soft matters (e.g. microfilaments in cells), which can weaken the ability of materials to overcome local energy traps in granular modeling. Based on all-atom molecular dynamics modeling of microfilament fragments (G-actin clusters), a new stochastic thermostat algorithm is developed to retain the representation of thermodynamic properties of microfilaments at extra coarse-grained level. The accuracy of this stochastic thermostat algorithm is validated by all-atom MD simulation. This new stochastic thermostat algorithm provides an efficient way to investigate the thermomechanical properties of large-scale soft matters.

Keywords: Thermomechanical, Coarse-grained, Microfilaments, Actin, Soft matter

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1. Introduction

Instead of relatively rigid materials that can be characterized in classic mechanics, soft matters consists of flexible material components whose mechanical performances can be significantly affected by its thermodynamic behaviors [1]. Molecular modelling approach provides a suitable way for the modeling of soft matters based on the truth that the internal entropic motion is benefiting the macroscale mechanical behaviors [2]. However, the length scale of soft matters in all-atom (AA) modeling is only hundreds of nanometers [3], which is limited to explore the overall performance of soft matters that consist of enormous randomly crosslinked chains/fibers at microscale. In order to enlarge the length scale of soft matters modeling, different coarse-grained (CG) strategies have been developed to describe the mechanical deformation of both organic and inorganic materials in terms of chemistry and physics [4-6].

Depending on the research objectives, there are two main strategies to develop corresponding CG modeling parameters: thermodynamic matching [7] and mechanical properties matching [8]. In order to guarantee the reliability of mechanical modeling of soft matters, we herein discuss the later strategy specifically. As a typical organic soft matter, microfilament is specifically investigated in this paper as a typical application. Microfilament network plays critical roles in eukaryotic cellular processes such as cell cytokinesis, spreading and migration [9], determining the fate of living cells [10-12]. *in-vivo* biomechanics experiments on single microfilaments are difficult to be carried out at molecular level due to the limits of experimental techniques and ethical constraints. Molecular dynamics (MD) simulation has been developed to reveal the conformational changes in actin monomers, which provides insights into the molecular mechanisms of the metabolism in association to microfilaments dynamics [13]. A large scale coarse-grained (CG) strategy for microfilaments modeling has been proposed to study the mechanical properties of microfilament networks at microscale [8]. Each simulation bead in this CG model is made up of two neighboring G-actin monomers and the mechanical deformation of microfilament networks are evaluated based on the interaction between simulation beads. In this CG modeling strategy, there is no need to adjust the force constant with respect to the effective bond lengths, and the mechanical behaviors of microfilament are to uncomplicated be unified with AA-MD characterization by defining proper force constants between simulation beads [8]. However, each bead in this CG strategy consists of more than 700 amino acids, which is far more than the typical ‘one-bead’ CG strategy whose simulation bead only represents one amino acids [14]. The thermal dynamic information of each physical atom in AA modeling is described by energy equipartition theorem [15], in which the mean kinetic energy of each harmonic solid can be directly derived as,

$$E_k = \frac{3}{2} k_B T \tag{1}$$

where k_B is the Boltzmann constant and T is the absolute temperature of thermal bath, E_k is the kinetic energy of the high frequency harmonic motion of simulation beads. These random motions of single atoms due to entropic energy can lead to both the structural disorder and the random movement of G-actin monomers, which are potentially obscured on the simulation beads in CG modeling strategy. Hence, it is arguable whether CG model can fully reveal the thermal dynamic motions of microfilaments

by directly implementing the classical thermostat algorithm, i.e., Eq.(1). The thermodynamic motions of microfilaments, e.g. thermal fluctuations, can lead to wormlike configurations of microfilaments, which is significant to the biological activities and mechanical deformation of microfilaments [16]. An efficient thermostat algorithm in CG modeling of microfilaments is crucial to assist the theoretical exploration of the biophysical properties of cell structures (e.g. filopodia and lamellipodia) at microscale, where AA-MD characterization is difficult to be applied due to its computational cost.

In this paper, by analyzing the thermodynamic behaviors of microfilaments, we investigate the ability of classical thermostat algorithm for the characterization of internal dynamic motions of microfilaments in association to the mechanical deformation modeling. A new stochastic thermostat algorithm is therefore proposed and implemented in a large-scale CG modeling strategy to estimate the thermomechanical properties of microfilaments with respects to its hierarchical structures.

2. Thermodynamic characterization of microfilament fragment

In order to investigate the difference of thermodynamic predictions between AA and CG molecular dynamics (MD) simulation of microfilament, a small fragment of microfilament that consists of only four G-actin monomers are at first studied. The F-actin crystallography 2ZWH [17] is adopted in the AA-MD characterization. The AA simulations are performed in Gromacs [18] with the force field of all-atom optimized potentials for liquid simulations (OPLS-AA) [19] in isothermal–isobaric (NPT) ensemble at the temperature of 303K (Berendsen method [15]) and the pressure of one bar (Parrinello-Rahman method [20]). Simple point-charge (SPC) water model [21] is used to explicitly consider the effects from solvent environment. The time step of AA-MD simulation is 2 femtoseconds and the simulation duration is 100 picoseconds. The longitudinal stiffness of a single microfilament is 43pN/nm [22] and the angular stiffness is 5.3×10^4pN·nm/rad^2 [8]. The equilibrium distance between simulation beads is 5.6nm and the equilibrium angle between adjacent bonds is 180^o. The CG-MD simulations are performed in Lampps [23] by utilizing the aforementioned harmonic potential energy equation. The temperature in CG-MD simulation is controlled at 303K by Langevin dynamics [24]. In the Langevin dynamics algorithm, two terms are added to the force calculation on each particle: viscous damping term due to solvent and a randomly bumping term due to temperature. The combination of these two terms is $F_d = -mv/C_d + \sqrt{mk_BT/dtC_d}$. Where, m is the mass of particle, v is the velocity of particle, dt is the time step. C_d is the damping factor with a time unit, which determines how rapidly the temperature is relaxed in the simulation. This C_d is the only flexible parameter that needs to be set up in the simulation. This parameter has dependency on the natures of both solvent and material particle. Based on the viscosity of water at 303K and the mass/diameter of G-actin clusters, C_d is estimated to be 1fs. The time step and modeling time in CG-MD simulation are all the same with AA-MD simulation. All the molecular visualization work are finished by using visual molecular dynamics (VMD) [25].

Fig. 1 provides the illustration of the aforementioned simulation models of microfilament fragment (both AA and CG level) and compared the longitudinal thermal fluctuation results from AA and CG level MD simulations. The configuration of microfilaments is rapidly equilibrated by using the CG modeling strategy for microfilaments. The molecular simulation model is

simplified from 163 thousands atoms (AA-MD simulation) to only two mass beads (CG-MD simulation, which saves enormous computational resources). However, the variation of filament length with regards to modeling time in CG-MD simulation is not significant compared to AA-MD simulation, which indicates that the thermodynamic motion of microfilament fragment is mostly missed in CG-MD simulation. This oversimplified CG-MD modeling technique with classical thermostat algorithm is sufficient to obtain stable conformation of microfilament fragment under mechanical boundary constrains [8], but inadequate in predicting the longitudinal thermal fluctuations. These results validated our concerns in the thermomechanical characterization of microfilaments by utilizing a highly CG modeling strategy.

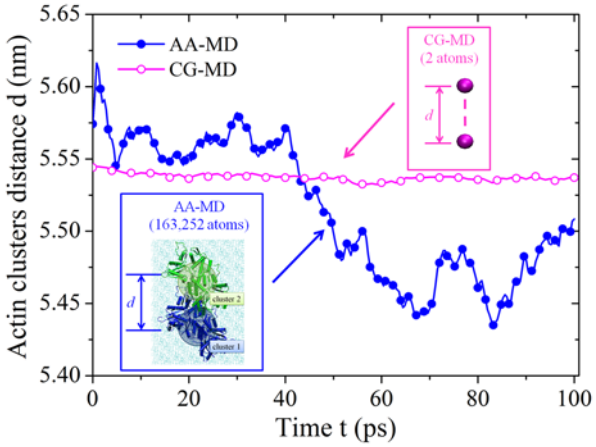

Fig. 1. The clusters distance in AA-MD (blue solid circle) and CG-MD (red hollow circle) simulations. The AA-MD simulation is finished by using 12 CPUs on HP Z600 workstation (Intel X5620, 2.67CHz) and the CG-MD simulation is finished by using single processor (Intel E8600, 3.3GHz). The calculation time for AA-MD simulation is 2 hours and four minutes, while the CG-MD simulation takes less than one second.

The force applied on each atom in the molecular system includes the interatomic action force, the damping effects from solvent and the random bumping due to temperature. Compared to the AA model of a molecular system, the interatomic forces and damping effects are similar to that in AA model based on the nature of these two terms. However, the temperature bumping effects present a different characteristic. All the atoms in one CG particle have their unique velocity vectors that are randomly distributed. Molecular resonance (violent oscillation of CG particles) will take place when the random velocity vectors of atoms present similar patterns in the same CG particle. The molecular resonance can increase the intensity of thermal fluctuation of particles in the modelling of soft matters. This characteristic =results in the difference of fluctuation prediction in AA and CG models, but cannot be described directly by the classical theorem of energy equipartition (i.e. Eq (1)). Specific thermostat algorithm for this CG modeling strategy is needed to accurately predict the thermodynamic behaviors of microfilaments related cell structures at microscale.

3. New stochastic thermostat algorithm

The kinetic energy of G-actin clusters mass center, which directly reflect the thermodynamic of G-actin clusters, is quantified by both CG-MD and AA-MD simulations to understand the law of G-actin clusters dynamics in MD simulations. Based on these

molecular investigations, a new stochastic thermostat algorithm for large-scale CG-MD modeling of microfilament is proposed to improve the quality of thermomechanical characterizations.

3.1 G-actin clusters kinetic energy

The theatrical fundaments of actin clusters kinetic energy evaluation in both CG-MD and AA-MD simulations will be detailed in this section. In CG-MD simulation, the mean kinetic energy of each single G-actin cluster is defined as in Eq. (1). A dimensionless factor, k_t, can be calculated as a kinetic energy ratio to estimate the accuracy of thermostat algorithm, i.e.

$$k_t = \frac{2E_k}{3k_B T} \tag{2}$$

For direct CG-MD technique, this variable k_t is a constant of one, which is not changing during the whole simulation process. In AA-MD simulations, the Newtonian kinetic energy of G-actin cluster mass centre can be extracted from the co-momentum of all atoms that belong to this G-actin cluster:

$$\begin{cases} M\vec{V} = \sum_{i=1}^{n} m_i \vec{v}_i \\ E_k = \frac{1}{2} M (\vec{V} \cdot \vec{V}) \end{cases} \tag{3}$$

where M is the overall mass of a G-actin cluster (84 kDa) and $\vec{V}$ is the overall velocity vector of cluster mass centre. m_i and $\vec{v}_i$ respectively denotes the mass and velocity vector of atom i in the n atoms G-actin cluster.

Two simulation models, which respectively include one and four G-actin clusters, are adopted to track the thermodynamic motions of G-actin clusters in solvent. Fig. 2 provides the illustration of these two simulation models. The molecular simulations are of the same temperature and pressure parameters with aforementioned AA-MD simulations in last section.

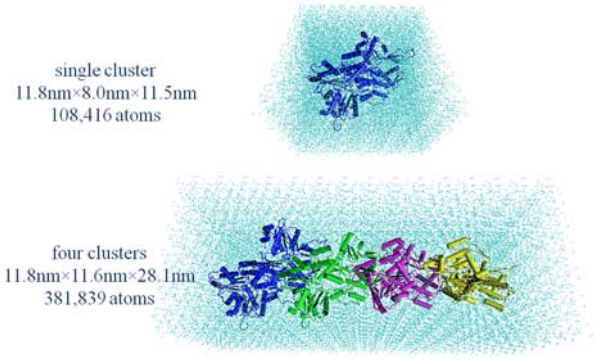

Fig. 2. The different simulation models of AA-MD microfilament thermal fluctuation simulations which respectively include one and four G-actin clusters. The cyan dots represent water molecules in the simulation.

3.2 Statistical property of k_t in AA-MD

The factor k_t is derived from AA-MD characterization results with respects to the modeling time. Fig. 3 provides the comparison of direct CG-MD technique and AA-MD simulation. It can be found that, the evaluations of G-actin clusters kinetic energy from

AA-MD characterizations are more scattered than the constant value from direct CG-MD technique, indicating the insufficiency of direct CG-MD simulations in predicting the thermodynamic behaviors of microfilament. In order to understand the statistic rule to which the kinetic energy of G-actin cluster belongs, the k_t results of a single G-actin cluster in solvent at 303K are extracted by utilizing AA-MD simulation. The statistical results are shown in Fig. 3(b). Gamma distribution is used to fit the distribution rule of scattered k_t values, and corresponding parameters of the distribution are also provided in Fig. 3(b).

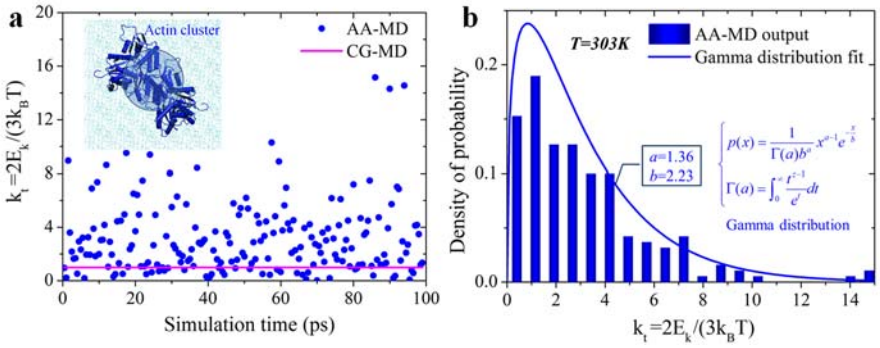

Fig. 3. The evaluation of k_t for a single G-actin cluster in water at 303K regarding modeling time. a: The scattered results of k_t with respect to simulation time; b: The Gamma distribution fitting of k_t results.

AA-MD simulations under different temperature from 50K to 303K are conducted to investigate the temperature dependency of k_t distribution. The Gamma distribution fitting results are given in Fig. 4. These distribution parameters, including shape parameter a, scale parameter b and expectation E of the distribution, are approximately constant in the temperature domain, which indicates the temperature dependency of the distribution parameters is not significant. In order to simplify the model, the average values of these three parameters are adopted in temperature domain to represent the overall distribution of k_t at different temperatures ranging from 50K to 303K.

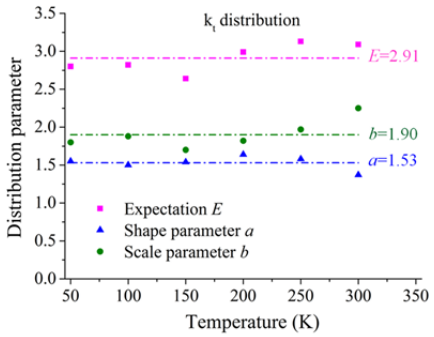

Fig. 4. The distribution parameters of k_t fitting at temperatures from 50K to 303K.

A larger model with 380 thousand atoms, which includes four G-actin clusters, is simulated to validate the reliability of the k_t distribution rule in multi-clusters system. Fig. 5 shows the Gamma distribution fitting of k_t for different G-actin clusters in the same simulation system. It can be found that different G-actin clusters follow similar distribution rules, and the Gamma distribution fitting can be a good candidate to describe the distribution of scattered k_t in this multi-clusters simulation system.

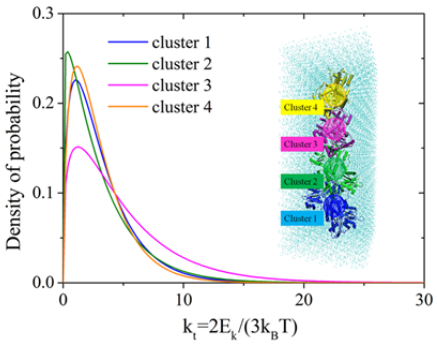

Fig. 5. The Gamma distribution fitting for the scattered variable k_t of different G-actin clusters from AA-MD simulation of microfilament fragment with four G-actin clusters.

3.3 Stochastic thermostat algorithm

Based on discussions about the distribution rule to which the factor k_t belongs, a new stochastic thermostat algorithm is proposed to predict the thermodynamic motions of G-actin clusters in the CG model of microfilaments. The modified thermostat algorithm is defined as:

$$\begin{cases} E_k = k_t \dfrac{3}{2} k_B T \\ k_t \sim \Gamma(a = 1.53, b = 1.9) \end{cases} \tag{3}$$

k_t is a variable that is changing over the modeling time (Fig. 3). The variation of this time dependent parameter (k_t) belongs to the aforementioned Gamma distribution, as given in Eq. (3). The distribution parameters, i.e. a and b, are obtained by averaging the fitting parameters of distributions in temperature domain (Fig. 4). In the current CG-MD simulations, the k_t is changed every one picosecond. It should be noted that, the distribution parameter a and b have dependency on the material and CG strategy, the values of a and b in Eq. (3) can only reveal the biophysical characteristics of microfilaments that adopts the aforementioned CG strategy. If the material or CG strategy is changed, proper modification of these distribution parameters is needed to retain the applicability of this stochastic thermostat algorithm for different soft matters.

4. Benchmarks and Validation

In order to validate the accuracy and efficiency of this new stochastic thermostat algorithm, the aforementioned question about the longitudinal thermal fluctuations of both short (11nm, 4 G-actin monomers) and long (72nm, 26 G-actin monomers) microfilament fragment is studied by implementing this new thermostat algorithm in the large-scale CG model[8].

According to Section 2, the variation of distance between G-actin clusters (each cluster denotes two G-actin monomers) is difficult to be accurately extracted from direct CG-MD simulation. In order to validate this newly proposed algorithm, the longitudinal fluctuation of a same microfilament fragment is investigated by the modified CG-MD technique and compared with AA-MD modeling results. As this new thermostat algorithm contains a random factors k_t, three different modified CG-MD simulation cases are conducted to illustrate the reliability of this new algorithm. These modified CG-MD simulation cases are of different k_t indexes that are randomly generated. Comparing with CG-MD technique with unmodified thermostat algorithm (pink

open circle), the modeling results of microfilament thermal fluctuation in this modified thermostat algorithm simulation presents larger variability, which is more close to AA-MD characterization (blue open square). The variation of amplitude with respects to modeling time would directly lead to random movements of microfilament fragments due to the thermal inputs to biological materials. However, the dynamic information would be lost in the direct CG-MD characterization, leading to the insufficiency of direct CG-MD strategy in modeling the thermomechanical properties of microfilament like, hierarchical soft materials.

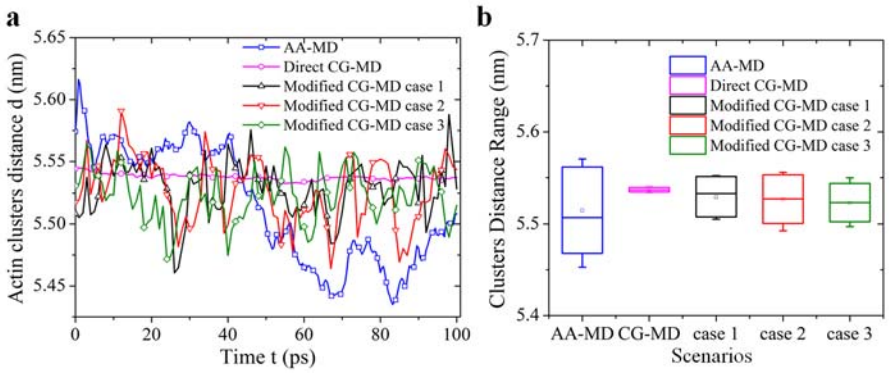

Fig. 6. Microfilament CG-MD modeling results by adopting the newly developed stochastic thermostat algorithm. a: the variation of G-actin clusters distance evaluated from different simulation strategies; b: the clusters distance ranges in a double clusters simulation system obtained from different simulation techniques.

As introduced, the three modified CG-MD cases (black up triangle, red down triangle and olive diamond) are of different k_t indexes, however, all lead to similar profiles of fluctuation ranges, indicating that the stochastic thermostat is reliable, even brought in randomly generated indexes of factor k_t. The computational duration of this simulation with modified CG-MD technique is less than one second on single processer for this small microfilament fragment. Comparing with the computational recourses needed by AA-MD method, this modified CG modeling strategy can used limited resources to obtain relatively reliable thermomechanical evaluation of a small microfilament fragment that consists of four G-actin monomers.

Another benchmark study is conducted to validate the accuracy and efficiency of this modified algorithm for longer microfilaments. Two F-actin helical repeats that includes 26 G-actin monomers are chosen for these scenarios. The total length of the filament is 72nm, and we chose the distance between the two G-actin clusters on microfilament ends as the reference variable. The absolute value of this distance is around 5.5nm less than the length of microfilament because of the size of the cluster (Fig. 7). The simulation conditions are all the same with abovementioed AA-MD simulation, except that the modeling time is extended to 1ns. The full atom simulation model consists of more than one million (1, 171, 472) atoms. The duration of AA-MD calculation is 49.5 hours with 12 CPUs on HP Z600 workstation (Intel X5620, 2.67CHz). Three sets of k_t indexes are adopted to study the numerical reliability of this newly developed algorithm (Fig. 7, black, red and olive). This results from CG-MD modeling scenarios with modified thermostat algorithm shows larger variation of thermal fluctuation, which is more consistent with AA-MD characterization results (blue solid square) compared with direct CG-MD modeling (magenta solid circle).

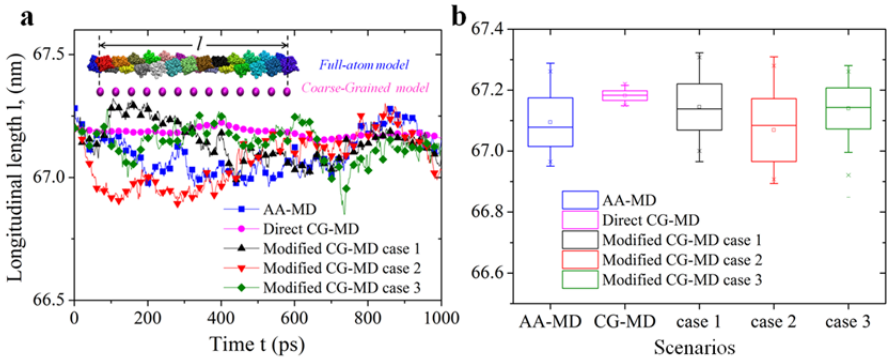

Fig. 7 The longitudinal thermal fluctuation of 72nm long microfilament from both AA-MD simulation and CG-MD simulation. a: the variation of longitudinal length from different simulation strategies; b: the thermal fluctuation ranges of a 72nm long microfilament obtained from different simulation techniques.

The computational time for the CG-MD simulation is only 10 seconds with one CPU (Intel E8600, 3.3GHz), which is far less than the 49 hours computational time of AA-MD simulation. The efficiency of this modified CG-MD method indicated that, this simulation strategy can be applied to large-scale, complex microfilament networks to investigate its dynamic behaviors due to thermal energy inputs. This CG model of microfilaments can be extended to three dimensional networks at microscale that is the actual size of cell structure, which is difficult for AA-MD method to handle with nowadays computational capability.

5. Discussion

MD simulation of soft matters has advantages in investigating their dynamic characteristics by considering the random motions of independent atoms due to thermal excitation. However, AA-MD simulation is inadequate to be applied to large-scale soft matters for studying thermodynamic behaviors due to the limit of computational capability. Continuum mechanics modeling has advantages in characterizing mechanical deformation of micro/macro scale materials, but is inadequate in capturing the associated internal entropic motions. As a bridging method, CG level granular simulation is necessary for the biophysical modeling of soft matters based on its natures in both static and dynamic characterizations. By simplifying the definition of simulation beads, CG models can improve the computational efficiency of MD simulation. Take the CG model of microfilaments for example: this CG model ignores conformational changes in each G-actin monomer while only focusing on the global motion of a G-actin cluster that consists of two monomers, approximately seven thousand atoms. Even though the computational efficiency of biophysical simulation can be improved, direct CG model is limited in the characterization of internal thermodynamic motions, because the dynamic behaviors of simulation beads in MD simulation have both enthalpic and entropic effects.

While upgrading the length scale of simulation models by decomposing stress fibers to be strings of CG beads, the information of high frequency motion of atoms inside each simulation bead will be obscured in CG methods. These stochastic motions of single atoms can lead to spontaneous behaviors of macromolecules, which is a long term response of biological materials. However, these time dependent properties of gel like soft matters are still challenges for different modelling methods, such as MD method and soft glass rheology (SGR) [26]. The challenge mainly lies in the following two points. First, the temporal scale of the methods is not large enough to describe the slow and time dependent properties of materials. Compared to picosecond scale of AA-MD

method, the temporal scale of this CG method can be extended to a few microseconds. However, there is still a long way to go for solving the long term response of soft matters which can take a few hours to finish. Second, another challenge for the modeling of soft matters lies in the local energy traps, whose depth are much larger than the thermal energy k_BT [27]. With understandings of the characteristics of macromolecular thermodynamics in this paper, the thermal fluctuations of the molecular clusters in soft matters are usually underestimated by adopting classical thermostat algorithm. This underestimation can weaken the ability of flexible materials to transform between local energy traps, which explains the reason why 'noise' or 'effective temperature' is needed to excite the material in SGR modeling. We note that, with assistance of the aforementioned kinetic energy ratio k_t, the thermodynamic behaviors of soft matters can be efficiently amplified to overcome the corresponding local energy traps in the thermomechanical modeling. In summary, our modified CG method can improve the ability of the prediction of phase changes in soft matter from the viewpoints of both energy and temporal scale. However, the method still has difficulties in fully exploring the rheology properties of gel like soft matters due to the limit of their absolutely large temporal scale, at which slow dynamics happens.

Based on the abovementioed claims, similar modification of thermostat algorithm should be made in all other attempts of building oversimplified CG models for soft matters at extra-large scales. This new algorithm can improve the capability of CG modeling in capturing thermomechanical properties of biological materials with hierarchical structures. Using this newly developed stochastic thermostat algorithm, CG-MD modeling method is competent to model the thermodynamic properties of soft matters in association tp the mechanical deformation modeling. Compared to AA-MD characterization, this modified CG-MD modeling strategy can significantly reduce the computational cost while efficiently retaining the ability of biophysical properties of soft biological materials with hierarchical structures.

6. Conclusions

A new stochastic thermostat algorithm is proposed to overcome the incapability of highly coarse-grained (CG) models of microfilaments in thermodynamic prediction. This newly developed algorithm can efficiently predict the thermodynamic properties of microfilament in association to the modeling of mechanical deformation. A statistical factor k_t, which belongs to Gamma distribution, is implemented in the relationship between temperature and kinetic energy. According to the characterization of longitudinal thermal fluctuations of both short (11nm, 4 G-actin monomers) and long (72nm, 26 G-actin monomers) microfilament fragments, this modified method can obtain more reliable thermodynamic behaviors compared to direct CG-MD modeling. By using this new stochastic thermostat algorithm, the computational efficiency can be significantly improved. This new stochastic thermostat algorithm provides an efficient and accurate way to investigate the biophysical properties of large-scale soft matters with hierarchical structures.

Acknowledgements

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Reference

[1] P.G. de Gennes, Soft Matter, Science, 256 (1992) 495-497.

[2] M. Karplus, J.A. McCammon, Molecular dynamics simulations of biomolecules, Nat. Struct. Mol. Biol., 9 (2002) 646-652.

[3] T. Splettstoesser, K.C. Holmes, F. Noé, J.C. Smith, Structural modeling and molecular dynamics simulation of the actin filament, Proteins: Struct., Funct., Bioinf., 79 (2011) 2033-2043.

[4] A. Gautieri, A. Russo, S. Vesentini, A. Redaelli, M.J. Buehler, Coarse-grained model of collagen molecules using an extended MARTINI force field, J. Chem. Theory Comput., 6 (2010) 1210-1218.

[5] R.E. Rudd, J.Q. Broughton, Coarse-grained molecular dynamics: Nonlinear finite elements and finite temperature, Physical Review B, 72 (2005) 144104.

[6] X.-Y. Ji, X.-Q. Feng, Coarse-grained mechanochemical model for simulating the dynamic behavior of microtubules, Physical Review E, 84 (2011) 031933.

[7] J.W. Chu, G.A. Voth, Coarse-grained modeling of the actin filament derived from atomistic-scale simulations, Biophys. J., 90 (2006) 1572-1582.

[8] T. Li, Y.T. Gu, X.-Q. Feng, P.K.D.V. Yarlagadda, A. Oloyede, Hierarchical multiscale model for biomechanics analysis of microfilament networks, J. Appl. Phys., 113 (2013) 194701-194707.

[9] T.D. Pollard, Mechanics of cytokinesis in eukaryotes, Curr. Opin. Cell Biol., 22 (2010) 50-56.

[10] D.A. Fletcher, R.D. Mullins, Cell mechanics and the cytoskeleton, Nature, 463 (2010) 485-492.

[11] T. Li, A. Oloyede, Y.T. Gu, F-actin crosslinker: A key player for the mechanical stability of filopodial protrusion, J. Appl. Phys., 114 (2013) 214701-214705.

[12] G.-K. Xu, X.-Q. Feng, H.-P. Zhao, B. Li, Theoretical study of the competition between cell-cell and cell-matrix adhesions, Physical Review E, 80 (2009) 011921.

[13] J.W. Chu, G.A. Voth, Allostery of actin filaments: molecular dynamics simulations and coarse-grained analysis, Proc. Natl. Acad. Sci. U. S. A., 102 (2005) 13111.

[14] V. Tozzini, Coarse-grained models for proteins, Curr. Opin. Struct. Biol., 15 (2005) 144-150.

[15] H.J.C. Berendsen, J.P.M. Postma, W.F. Van Gunsteren, A. DiNola, J. Haak, Molecular dynamics with coupling to an external bath, The Journal of Chemical Physics, 81 (1984) 3684-3690.

[16] L. Le Goff, O. Hallatschek, E. Frey, F. Amblard, Tracer Studies on F-Actin Fluctuations, Phys. Rev. Lett., 89 (2002) 258101.

[17] T. Oda, M. Iwasa, T. Aihara, Y. Maéda, A. Narita, The nature of the globular-to fibrous-actin transition, Nature, 457 (2009) 441-445.

[18] H.J.C. Berendsen, D. van der Spoel, R. van Drunen, GROMACS: A message-passing parallel molecular dynamics implementation, Comput. Phys. Commun., 91 (1995) 43-56.

[19] W.L. Jorgensen, D.S. Maxwell, J. Tirado-Rives, Development and Testing of the OPLS All-Atom Force Field on Conformational Energetics and Properties of Organic Liquids, J. Am. Chem. Soc., 118 (1996) 11225-11236.

[20] M. Parrinello, A. Rahman, Polymorphic transitions in single crystals: A new molecular dynamics method, J. Appl. Phys., 52 (1981) 7182-7190.

[21] H. Berendsen, J. Postma, W. Van Gunsteren, J. Hermans, Interaction models for water in relation to protein hydration, Intermolecular forces, 331 (1981) 331-338.

[22] H. Kojima, A. Ishijima, T. Yanagida, Direct measurement of stiffness of single actin filaments with and without tropomyosin by in vitro nanomanipulation, Proceedings of the National Academy of Sciences, 91 (1994) 12962-12966.

[23] S. Plimpton, Fast Parallel Algorithms for Short-Range Molecular Dynamics, J. Comput. Phys., 117 (1995) 1-19.

[24] G.E. Uhlenbeck, L.S. Ornstein, On the Theory of the Brownian Motion, Physical Review, 36 (1930) 823-841.

[25] W. Humphrey, A. Dalke, K. Schulten, VMD: visual molecular dynamics, J. Mol. Graphics, 14 (1996) 33-38.

[26] P. Sollich, F. Lequeux, P. Hébraud, M.E. Cates, Rheology of Soft Glassy Materials, Phys. Rev. Lett., 78 (1997) 2020-2023.

[27] O. Lieleg, J. Kayser, G. Brambilla, L. Cipelletti, A.R. Bausch, Slow dynamics and internal stress relaxation in bundled cytoskeletal networks, Nat. Mater., 10 (2011) 236-242.